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Michelle Hobson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: E. Rebar *et al.* Application No.: 10/055,711 Filed: January 22, 2002 For: MODIFIED ZINC FINGER BINDING PROTEINS	Examiner: Jennifer A. Dunston Group Art Unit: 1636 Confirmation No.: 6236

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is filed pursuant to 37 C.F.R. § 41.37 and is in response to the Final Office Action mailed April 27, 2009 and Advisory Action mailed July 7, 2009. A Notice of Appeal was received by the Office on July 27, 2009, making an Appeal Brief due by September 27, 2009. Accordingly, this Appeal Brief is timely filed.

REAL PARTY IN INTEREST

Sangamo BioSciences, Inc. is the assignee of record in this case by virtue of an assignment recorded on April 24, 2002 at Reel 012622, Frame 0897. Thus, Sangamo BioSciences, Inc. is the real party in interest.

RELATED APPEALS AND INTERFERENCES

Appellants note that an Appeal Brief was filed on November 27, 2006 in U.S. Serial No. 10/470,180 (now U.S. Patent No. 7,262,054) that may be considered relevant to the instant case on appeal.

STATUS OF THE CLAIMS

Pending: claims 1, 23-28, 30-48 and 52-57

Withdrawn: 1, 23, 24, 33-35, 38, 42-48 and 52

Canceled: claims 2-22, 29, 49 and 58-61

Rejected: claims 25-28, 30-32, 36, 37, 39-41 and 53-57

Appealed: claims 25-28, 30-32, 36, 37, 39-41 and 53-57

STATUS OF THE AMENDMENTS

No amendments to the claims were made after final. Therefore, the claims on appeal are as shown in the Claims Appendix.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 30 is drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component (page 4; lines 1-2 page 18, lines 24-31). The non-canonical zinc finger component contains a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, in which at least one of the zinc coordinating residues is a histidine residue and at least one of the zinc coordinating residues is a cysteine residue (page 4, lines 6-14; page 46, lines 1-9; Table 1 on page 47). In addition,

the non-canonical zinc finger component comprises 1, 2, 3, 4, 6 or 7 amino acids between the two carboxy-terminal zinc coordinating residues and 2, 3 or 4 amino acids between the two amino-terminal zinc coordinating residues (page 46, lines 1-9; Table 1 on page 47). The non-canonical zinc-finger binding domain protein comprises a recognition helix of at least 7 amino acids in length, which recognition helix is non-naturally occurring and is engineered to bind to a target nucleic acid sequence in a plant cell (page 49; Table 2 on page 51; Table 3 on page 54).

Claim 25 depends from claim 30 and further specifies that the target sequence is a promoter sequence (page 4, lines 4-5).

Claim 26 depends from claim 30 and further indicates that the zinc finger binding protein comprises three zinc finger components (page 3, lines 28-30).

Claim 27 depends from claim 30 and further specifies that the target sequence comprises about 9 to about 14 contiguous base pairs (page 59, lines 13-14).

Claim 28 depends from claim 26 and further indicates that the third zinc finger component comprises a non-canonical zinc finger component (page 3, lines 30-31).

Claim 31 depends from claim 30 and further specifies that an expression vector comprises the polynucleotide of claim 30 (page 4, lines 28-29).

Claim 32 depends from claim 30 and further specifies that a host cell comprises the polynucleotide of claim 30 (page 4, lines 28-29).

Claim 39 depends from claim 30 and further indicates that the isolated polynucleotide further encodes a functional domain (page 4, lines 21-22).

Claim 36 depends from claim 39 and further specifies that the functional domain is an activation domain (page 4, lines 24-25).

Claim 37 depends from claim 36 and further specifies that the activation domain is selected from the group consisting of maize C1, VP16, p65 subunit of NF-kappa B, and VP64 (page 4, lines 24-25).

Claim 40 depends from claim 39 and further indicates that an expression vector comprises the polynucleotide of claim 39 (page 4, lines 28-29).

Claim 41 depends from claim 39 and further indicates that a host cell comprises the polynucleotide of claim 39 (page 4, lines 28-29).

Claim 53 is drawn to a composition comprising a polynucleotide according to claim 39 and a pharmaceutically acceptable excipient (page 5, lines 11-12).

Claim 54 depends from claim 26 and specifies that the first zinc finger component comprises a non-canonical zinc finger component (page 46, lines 1 and 6).

Claim 55 depends from claim 30 and further indicates that the zinc finger binding protein comprises four zinc finger components (page 4, lines 15-17; page 16, lines 15-16; page 20, line 17).

Independent claim 56 is drawn to an isolated polynucleotide encoding a non-naturally occurring zinc-finger binding protein comprising a non-canonical zinc finger component (page 4; lines 1-2 page 18, lines 24-31). The non-canonical zinc finger component contains a beta turn comprising two amino-terminal zinc coordinating cysteine and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, in which one of the carboxy-terminal zinc coordinating residues is a histidine residue and one of the carboxy-terminal zinc coordinating residues is a cysteine residue (page 4, lines 6-14; page 46, lines 1-9; Table 1 on page 47). In addition, the non-canonical zinc finger component comprises 2 amino acids between the two amino-terminal zinc coordinating cysteine residues (pages 19-20); and the protein comprises a non-naturally occurring recognition helix that is engineered to bind to a target nucleic acid sequence (page 49; Table 2 on page 51; Table 3 on page 54).

Claim 57 depends from claim 56 and further specifies that the carboxy-terminal zinc coordinating histidine residue is amino terminal to the carboxy-terminal zinc coordinating cysteine residue (Table 1 on page 47).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 25-28, 30-32, 36-37, 39-41 and 53-57 are unpatentable under 35 U.S.C. § 103(a) in view of U.S. Patent No. 7,151,201 (hereinafter "Barbas '201") in view of Filippova (1996) *Mol. Cell Biol.* 16(6):2802-2813 (hereinafter "Filippova").

B. Whether claims 25-28, 30-32, 36, 39-41 and 53-57 are unpatentable under 35 U.S.C. § 103(a) in view of U.S. Patent No. 7,329,728 (hereinafter "Barbas '728") in view of Filippova.

C. Whether claim 37 is unpatentable under 35 U.S.C. § 103(a) over Barbas '728 in view of Filippova and further in view of Guyer et al. (1998) *Genetics* 149:633-639 (hereinafter "Guyer").

ARGUMENTS

A. The claims are non-obvious over Barbas '201 and Filippova

Claims 25-28, 30-32, 36-37, 39-41 and 53-57 remained rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 7,151,201 (hereinafter "Barbas '201") in view of Filippova (1996) *Mol. Cell Biol.* 16(6):2802-2813 (hereinafter "Filippova"). (Final Office Action, pages 3-7 and Advisory Action, pages 2-4). Barbas '201 was again cited for allegedly teaching alteration of any zinc finger protein framework and Filippova was cited for teaching the human CTCF protein, in which the 11^{th} zinc finger has a CCHC structure. *Id.*

In response to Appellants' arguments that Barbas '201 and Filippova do not establish that it was predictable to modify the recognition helix region of C3H zinc fingers having the claimed structure to bind to a gene in a plant cell, it was asserted that the references do in fact teach the claimed elements were predictable (Advisory Action, pages 3-4):

> Barbas, III et al. teach that any naturally occurring zinc finger protein can be used as a framework (or backbone) to derive a non-naturally occurring zinc finger with DNA binding specificity determined by alterations to the alpha helix of the zinc finger by using known design rules (e.g., column 10, lines 55-67; col. 11, lines 14-35; column 19, lines 28-34 and 57; column 21, lines 8-39; column 22, line 51 to column 25, line 9). Thus, the teachings of Barbas, III et al are not limited to the modification of the C3H finger taught by Terol. Furthermore, the rejection of record is not based upon the C3H protein disclosed by Terol. Barbas, III et al teach the use of any zinc finger and define the term "zinc finger" to mean "a polypeptide having nucleic acid, e.g., DNA binding domains that are stabilized by zinc" (e.g. column 10, lines 55-57; column 18, lines 47-49). The zinc finger of Filippova et al meets the definition of "zinc finger" provided by Barbas III et al.

For the reasons of record and set forth in this Appeal Brief, it remains the case that Barbas '201 and Filippova, alone or in combination, do not teach or suggest the claimed subject matter. It is axiomatic that in order to establish obviousness of a claimed invention, all the features of the claims must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Thus, in the pending case, the combination of references must disclose a polynucleotide that encodes a non-naturally occurring zinc finger protein that includes a non-canonical (non-Cys2His2) zinc finger with the recited number of amino acids between zinc coordinating residues and in which the recognition helix of the non-canonical zinc finger has been altered to bind to a target site in a plant gene.

In the case on appeal, the Examiner's rejection appears to be based on the assertion that the teachings in Barbas '201 regarding altering the recognition helices of any naturally occurring zinc finger within the context of its naturally occurring framework can be applied to Filippova's CTCF protein to result in a molecule as claimed.

It is undisputed that Barbas '201 teaches only that the recognition helices can be altered in the context of the naturally occurring protein as a whole (Barbas '201, column 11, lines 14-19; column 20, lines 3-10; column 21, lines 8 to 20; column 22, lines 51-60; column 22, lines 61 to column 23, line 61; column 23, lines 8-11; column 23, lines 12-15; column 23, lines 23-25; emphasis added)

> As used herein, "**framework (or backbone)** derived from a naturally occurring zinc finger protein" means that the protein or peptide sequence within the naturally occurring zinc finger protein that is involved in non-sequence specific binding with a target nucleotide sequence is **not** substantially changed from its natural sequence. ....
>
> The zinc finger polypeptides used in the present method can be engineered to recognize a selected target site in the gene of choice. Typically, a **backbone** from **any** suitable C2H2-ZFP, such as SPA, SPIC, or ZIF268, is used as the scaffold for the engineered zinc finger polypeptides (see, e.g., Jacobs, EMBO J. (1992) 11:4507; and Desjarlais & Berg, Proc. Natl. Acad. Sci. USA (1993) 90:2256–2260). A number of methods can then be used to design and select a zinc finger polypeptide with high affinity for

its target. A zinc finger polypeptide can be designed or selected to bind to any suitable target site in the target gene, with high affinity.

A useful zinc finger **framework** is that of ZIF268 (see WO00/23464 and references cited therein), however, others are suitable. Examples of known zinc finger nucleotide binding polypeptides that can be truncated, expanded, and/or mutagenized in order to change the function of a nucleotide sequence containing a zinc finger nucleotide binding motif includes TFIIIA and zif268. Other zinc finger nucleotide binding proteins are known to those of skill in the art. The murine CYS2-HiS2 zinc finger protein Zif268 is structurally well characterized of the zinc finger proteins (Pavletich and Pabo, *Science* (1991) 252:809–817; Elrod-Erickson et al., *Structure* (*London*) (1996) 4:1171–1180; and Swirnoff et al., *Mol. Cell. Biol*. (1995) 15:2275–2287).

In a specific embodiment, the zinc finger protein used in the present methods comprises a **framework (or backbone)** derived from a naturally occurring zinc finger protein. Framework (or backbone) derived from any naturally occurring zinc finger protein can be used. For example, the zinc finger protein comprises a framework (or backbone) derived from a zinc finger protein comprising a C2H2 motif can be used. Preferably, the protein or peptide sequence within the β sheet of the C2H2 motif is not substantially changed, or not changed, from its natural sequence.

In another specific embodiment, the zinc finger protein used in the present methods comprises a **framework (or backbone)** derived from a zinc finger protein that is naturally functional in plant cells. For example, the zinc finger protein used in the present methods can comprise a C3H zinc finger (Terol et al., Gene, 260(1–2):45–53 (2000)), a QALGGH motif (Takatsuji, Plant. Mol. Biol., 39(6):1073–8 (1999)), a RING-H2 zinc finger motif (Jensen et al., FEBS Lett., 436(2):283–7 (1998)), a 9 amino acid C2H2 motif (Chou et al., Proc. Natl. Acad. Sci. USA, 95(9):5293–8 (1998)), a zinc finger motif of Arabidopsis LSD1 (Dietrich et al., Cell, 88(5):685–94 (1997)) and a zinc finger motif of BBF/Dof domain proteins (De Paolis et al., Plant J., 10(2):215–23 (1996)).

In another specific embodiment, the zinc finger protein used in the present methods comprises **a framework (or backbone)** derived from a zinc finger protein that is known in the art as of Jan. 19, 2001.

For example, the zinc finger protein used in the present methods can comprise a **framework (or backbone)** derived from the zinc finger protein disclosed in the following U.S. patents and PCT patent publications: ...

> The zinc finger protein used in the present methods can also comprise a **framework (or backbone)** derived from the zinc finger protein disclosed in the following references: ...

Thus, the issue is whether the references (or state of the art as a whole) teach that recognition helix within any framework can be altered as described in Barbas '201 and the resulting protein would necessarily bind to a target site in a plant gene, as claimed. Specifically, when using Filippova's CTCF as the framework (backbone), the skilled artisan must have been taught by Barbas '201 that altering the recognition helix of the only C3H finger (the 11th finger) of CTCF would result in a protein in which this altered C3H finger bound to a target site in a plant gene.

However, such teachings are completely lacking from Barbas '201, Filippova and the state of the art. The only frameworks that Barbas actually shows are functional are canonical Cys2His2 proteins, particularly Zif268 and/or TFIIIA. *See, e.g.,* Examples of Barbas.

For its part, Filippova teaches away from using CTCF as a framework because of the fact this 11-finger framework (backbone) uses different finger combinations to bind to a variety of different target sites (Filippova, Abstract):

> Although there is 100% sequence identity in the DNA binding domains of the avian and human CTCF proteins, the regulatory sequences recognized by CTCF in the chicken and human *c-myc* promoters are cleavage diverged. ... Gel shift assays utilizing successively deleted Zn finger domains indicate that CTCF Zn fingers 2 to 7 are involved in binding to the chicken *c-myc* promoter, while fingers 3-11 mediate CTCF binding to the human promoter.

Thus, Filippova teaches that altering the recognition helix of finger 11 of CTCF has no relevance to DNA binding of the protein, inasmuch as the only non-canonical finger (finger 11) is not necessarily involved in DNA binding.

Furthermore, additional publications by Barbas evidence that the skilled artisan believed that framework residues could impact binding and, as such, only when the

recognition helix of certain Cys2His2 frameworks were altered was binding function in any way predictable. *See, e.g.,* Barbas '728 (discussed in detail below) which teaches that altered recognition helices function only in certain frameworks (Barbas '728 col. 42, lines 19-24):

> The framework residues play a role in affinity and specificity. Thus, amino acid positions −2 to 6 of the DNA recognition helices are either grafted into a Zif268 (Pavletich et al. (1991) Science 252:809-817) or an Sp1C framework (Desjarlais et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:2256-2260).

Therefore, the alleged teaching in Barbas '201 that the recognition helix can be altered in any framework is untenable in view of the evidence of record. Barbas '201 only teaches how to use canonical zinc fingers in which all the fingers are involved in binding. Filippova clearly teaches that the CTCF framework is a complicated protein in which the lone non-canonical finger is not always involved in DNA binding functionality. Further evidence (Barbas '728) clearly establishes that the framework was considered relevant to binding and, as such, only certain canonical backbones were known to support DNA binding function of altered recognition helices. Thus, in view of the references and state of the art, the skilled artisan would have no reason to believe that altering the recognition helix (as described in Barbas '201) of the only non-canonical finger (the 11th finger) of CTCF would result in a protein with a non-canonical finger that bound to a target site in plant gene.

Accordingly, Barbas '201 and Filippova fail to teach or suggest the claimed elements (*e.g.,* a protein comprising a non-canonical finger with a recognition helix that is engineered to bind to a target site in a plant gene).

Furthermore, it is entirely unpredictable from the references and state of the art at the time of filing that altering the single non-canonical finger of Filippova would result in a functional protein. As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398; 82 USPQ2d 1385, 1397 (2007) and Patent Office Guidelines regarding determining obviousness issued in view of *KSR*, an obviousness rejection is only proper

when the proposed combination of elements results in a predictable outcome (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007, emphasis added):

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

Rather, the Supreme Court in *KSR* reiterated that an obviousness inquiry is fact-dependent and that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 82 UPSQ2d at 1389. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

In the instant case, there is no combination of Barbas '201 and Filippova that establishes that the proteins encoded by the claimed polynucleotides were a predictable use of allegedly known elements. As admitted by the Office and noted above, Barbas '201 fails to teach or suggest anything about non-canonical zinc finger domains set forth in claims 30 and claims dependent therefrom, namely zinc fingers having 2-4 amino acid residues between the amino terminal zinc coordinating residues and 1, 2, 3, 4, 6 or 7 amino acid residues between the carboxy terminal zinc coordinating residues. Thus, Barbas '201 fails to teach using C3H backbones of the claimed structure.

Furthermore, there is absolutely nothing in Barbas '201 that teaches it was predictable to modify the backbones and/or the recognition helices of Filippova's CTCF protein, including the lone C3H finger, to arrive at the claimed plant gene-binding proteins. Again, there is absolutely no evidence that altering the recognition helix region of the 11th finger of this protein would result in a protein that bound to DNA, let alone would result in a protein in which the altered non-canonical finger would bind to a target

site in a plant gene. Given that the 11th finger is not always involved in binding, the skilled artisan would not know that altering the recognition helix of this finger would result in a protein as claimed. Binding remains unpredictable even if all recognition helices are altered, for example, the protein may bind to a site using only fingers 2-7 (as in chickens). In this case, the protein does not include a non-canonical zinc finger with an engineered recognition helix that binds to a target sequence in a plant gene, as claimed.

For at least the foregoing reasons, withdrawal of the rejection is in order.

B. The claims are non-obvious over Barbas '728 and Filippova

Claims 25-28, 30-32, 36, 39-41 and 53-57 also remain rejected as allegedly obvious over U.S. Patent No. 7,329,728 (hereinafter "Barbas '728") in view of Filippova, as cited above. (Final Office Action, pages 7-10 and Advisory Action, pages 5-6). As with Barbas '201, it was acknowledged that Barbas '728 does not teach isolated polynucleotides encoding a non-canonical zinc finger protein as claimed. However, Filippova was again alleged to teach this element. *Id.*

In response to Appellants' arguments that Barbas '728 and Filippova do not teach a protein containing a non-canonical finger as claimed, it was asserted that Barbas '728 teaches altering the recognition helix region of any naturally occurring zinc finger protein and that Filippova's single C3H finger (11th finger of CTCF) "functions as a part of a zinc finger protein" and that the function of this non-canonical zinc finger domain of Filippova is "to bind DNA." (Advisory Action, page 5 and sentence bridging pages 5-6).

Appellants note there is no combination of Barbas '728 and Filippova that teaches or suggests the claimed molecules. Contrary to the Examiner's assertion, Barbas '728 clearly teaches that not any framework zinc finger backbone can be used with assurances that the recognition helix will bind to the predicted target site (see, Barbas '728, column 42, lines 19-24; col. 45, lines 15-21):

> The framework residues play a role in affinity and specificity. Thus, amino acid positions −2 to 6 of the DNA recognition helices are either

> grafted into a Zif268 (Pavletich et al. (1991) Science 252:809-817) or an Sp1C framework (Desjarlais et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:2256-2260).
>
> The framework residues may play a role in affinity and specificity. For helix grafting, amino acid positions −2 to 6 of the DNA recognition helices were either grafted into a Zif268 (Pavletich et al. (1991) Science 252:809-817) or an Sp1C framework (Desjarlais et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:2256-2260).

Simply put, Barbas '728 teaches away from using Filippova's CTCF framework by clearly teaching that it is entirely unpredictability that altering the recognition helix of frameworks other than canonical Zif268 or Sp1 a protein of known binding specificity would be produced.

Moreover, the Examiner's assertion that Filippova teaches that their single non-canonical finger "functions as part of their protein" to bind DNA is clearly in error. (Advisory Action, page 5 and sentence bridging pages 5-6). As noted above, Filippova is unambiguous that finger 11 of CTCF (the only non-canonical finger) is <u>not</u> involved in DNA binding in some instances. Thus, even if the recognition helix region of this non-canonical finger were altered, it is entirely unpredictable as to whether the protein as a whole and/or the individual finger would bind to its target site.

In sum, the references do not teach or suggest altering the recognition helix of Filippova's 11th finger of CTCF so as to bind to a target site in a plant gene and the references themselves establish that the skilled artisan would view such a modified CTCF protein as completely unpredictable in terms of DNA binding function. Thus, there is no combination of these references that teaches or suggests the claimed subject matter and the rejection cannot stand.

C. Claim 37 is non-obvious over the cited references

Claim 37 was rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Barbas '728 in view of Filippova and in further view of Guyer, which was cited as previously for allegedly disclosing GAL4-C1 fusion proteins. (Final Office Action, pages 10-12 and Advisory Action page 6). Barbas '728 and Filippova were cited as

above and Guyer was cited for teaching a hybrid transcription factor comprising the DNA binding domain of the *S. cerevisiae* GAL4 protein and the transcription activation domain of the maize C1. *Id.*

For the reasons detailed above, Barbas '728 and Filippova do not teach or suggest modification of the recognition helix region in zinc finger proteins containing a single non-canonical finger. To the contrary, Barbas '728 teaches that framework residues impact both DNA binding affinity and specificity and that only Zif268 or Sp1 backbones (both Cys2His2 fingered proteins) should be used. Guyer fails to cure the deficiencies of Barbas '728 and Filippova.

Thus, a *prima facie* case of obviousness has not been and cannot be established and the rejection of claim 37 should be withdrawn.

CONCLUSION

Appellants believe the claims are in condition for allowance and respectfully request that the Board reverse the Examiner and the claims proceed to allowance.

Respectfully submitted,

Date: September 24, 2009

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CLAIMS APPENDIX

25. The isolated polynucleotide of claim 30, wherein the target sequence is a promoter sequence.

26. The isolated polynucleotide of claim 30, wherein the zinc finger binding protein comprises three zinc finger components.

27. The isolated polynucleotide of claim 30, wherein the target sequence comprises about 9 to about 14 contiguous base pairs.

28. The isolated polynucleotide of claim 26, wherein the third zinc finger component comprises a non-canonical zinc finger component.

30. An isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein:

(i) said non-canonical zinc finger component contains a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, wherein at least one of the zinc coordinating residues is a histidine residue and at least one of the zinc coordinating residues is a cysteine residue;

(ii) the non-canonical zinc finger component comprises 1, 2, 3, 4, 6 or 7 amino acids between the two carboxy-terminal zinc coordinating residues and 2, 3 or 4 amino acids between the two amino-terminal zinc coordinating residues; and

(iii) the non-canonical zinc-finger binding domain protein comprises a recognition helix of at least 7 amino acids in length, wherein the recognition helix is non-naturally occurring and is engineered to bind to a target nucleic acid sequence in a plant cell.

31. An expression vector comprising the polynucleotide of claim 30.

32. An isolated host cell comprising the polynucleotide of claim 30.

36. The polynucleotide of claim 39, wherein the functional domain is an activation domain.

37. The polynucleotide of claim 36, wherein the activation domain is selected from the group consisting of maize C1, VP16, p65 subunit of NF-kappa B, and VP64.

39. An isolated polynucleotide according to claim 30 further encoding a functional domain.

40. An expression vector comprising the polynucleotide of claim 39.

41. An isolated host cell comprising the polynucleotide of claim 39.

53. A composition comprising a polynucleotide according to claim 39 and a pharmaceutically acceptable excipient.

54. The isolated polynucleotide of claim 26, wherein the first zinc finger component comprises a non-canonical zinc finger component.

55. The isolated polynucleotide of claim 30, wherein the zinc finger binding protein comprises four zinc finger components.

56. An isolated polynucleotide encoding a non-naturally occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein:

(i) said non-canonical zinc finger component contains a beta turn comprising two amino-terminal zinc coordinating cysteine and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, wherein one of the carboxy-

terminal zinc coordinating residues is a histidine residue and one of the carboxy-terminal zinc coordinating residues is a cysteine residue;

(ii) the non-canonical zinc finger component comprises 2 amino acids between the two amino-terminal zinc coordinating cysteine residues; and

(iii) the protein comprises a non-naturally occurring recognition helix that is engineered to bind to a target nucleic acid sequence.

57. The polynucleotide of claim 56, wherein the carboxy-terminal zinc coordinating histidine residue is amino terminal to the carboxy-terminal zinc coordinating cysteine residue.

EVIDENCE APPENDIX

No documents are attached to this appendix.

RELATATED PROCEEDINGS APPENDIX

As noted on page 2 of this Appeal Brief, Appellants note that an Appeal Brief was filed in U.S. Serial No. 10/470,180 (now U.S. Patent No. 7,262,054) on November 27, 2006. However, as this case was allowed prior to a Decision on Appeal being issued by the Board, no Decisions have been rendered by the Board in this case and no documents are attached to this Appendix.